

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau**AG**

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07B 61/00, B01J 19/00	A1	(11) International Publication Number: WO 98/47838 (43) International Publication Date: 29 October 1998 (29.10.98) WO 98/46549
(21) International Application Number: PCT/GB98/01063 (22) International Filing Date: 14 April 1998 (14.04.98) (30) Priority Data: 9707741.6 17 April 1997 (17.04.97) GB (71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): GARMAN, Andrew, John [GB/GB]; Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). PEARS, David, Alan [GB/GB]; Zeneca Specialties, Research Dept., The Heath, Runcom M9 8ZS (GB). (74) Agent: PHILLIPS, Neil, Godfrey, Alasdair; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: PROCESS FOR THE PREPARATION OF A CHEMICAL LIBRARY (57) Abstract A method for the preparation of a chemical library, which method comprises synthesising the library on a plurality of synthesis particles comprising random features, recording such features during library synthesis, so as to provide a chemical library on a plurality of synthesis particles and wherein the identity of library compound(s) associated with a synthesis particle is established by reference to the particle's random features.		

Best Available Copy

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PROCESS FOR THE PREPARATION OF A CHEMICAL LIBRARY

Chemical libraries are a powerful way of providing compounds for the identification of active compounds in pharmaceutical, agrochemical and related industries.

5 Chemical libraries may be assembled by a number of methods, including the 'combine/mix/divide', or split synthesis process described by Furka *et al* (Abstr. 14th Int. Congr. Biochem., Prague, Czechoslovakia, 1988, 5, 47; Int. J. Pept. Prot. Res, 1991, 37, 487-493) for creating libraries on polymer beads, in which each bead contains one discrete chemical species. The individual components of the library may be tested either still
10 attached to the polymer bead on which they were synthesised (Lam *et al*, Nature, 1991, 354, 82-84) or after cleavage from the bead (Salmon *et al*, Proc. Nat. Acad. Sci. USA, 1993, 90, 11708-11712). If tested while attached to the bead, or cleaved but physically associated with the bead, it is necessary to devise a method of identifying the chemical which is bound to any bead found to be biologically active in the test. Where this compound is a
15 polypeptide this may be achieved by Edman degradation, either directly or after cleavage from the bead (Lam *et al*, Bioorg. Med. Chem. Lett., 1993, 3, 419-424); oligo nucleotides may be identified by microsequencing techniques (Dower *et al*, Ann. Rep. Med. Chem., 1991, 26, 271-280). Other small molecules may be identified directly by electrospray, matrix-assisted laser desorption, or time-of-flight secondary ion mass spectrometry
20 techniques (Brummel *et al*, Analyt. Chem., 1996, 68, 237-42).

Researchers have attempted to identify peptides containing unnatural amino acids, which are not amenable to Edman degradation, by co-synthesising a second peptide chain comprising natural amino acids and using this as a sequenceable 'code' (Nikolaiev *et al*, Peptide Research, 1993, 6, 161-170), and others have used oligonucleotide chains as 'codes' to
25 identify the other ligands (Needels *et al*, Proc. Nat. Acad. Sci. USA, 1993, 90, 10700-10704), while mixtures of halogenated aromatic compounds have been used, incorporated in trace amounts at each stage of the synthesis, to form an identifiable (by gas chromatography) 'binary code' system for ligand definition (Borchardt and Still, J. Am. Chem. Soc., 1994, 116, 373-374). These methods have been reviewed extensively (Jacobs and Fodor, TIBTECH,
30 1994, 12, 19-26; Pavia *et al* (Eds), Bioorg. Med. Chem. Lett., 1993, 3, 381-470; Moos *et al*, Ann. Rep. Med. Chem., 1993, 28, 315-324; Gordon *et al*, J. Med. Chem., 1994, 37, 1233-

1251, and 1386-1401; K. D. Janda, Proc. Natl. Acad. Sci. USA, 1994, **91**, 10779-10785). An alternative to such chemical coding or tagging strategies has been the use of silicon chips in the form of radio frequency, or 'RF' tags, which, when associated with self-contained packets of polymer beads, can be used to store information about the chemical synthetic processes used to make a particular ligand, and hence by inference, the chemical structure of the resultant ligand (Moran *et al*, J. Am. Chem. Soc., 1995, **117**, 10787-10788; Nicolaou *et al*, Angew. Chem. Int. Ed. Engl., 1995, **34**, 2289-2291). A key advantage of this RF approach is that by using an essentially non-chemical tag, the risk of the vital stored information being affected, or at worst destroyed, by the chemical synthetic processes used to construct the ligand is considerably lessened. However, that risk of information corruption due to chemical or physical extremes is not zero. It is well-known in the microchip industry that certain types of otherwise convenient (e.g. EEPROM) silicon-based memory may not retain its data through all chemical processes, being potentially vulnerable to high temperatures and intense light levels.

15 It is clear that considerable effort has been applied to the compound identification problem, but that there are limitations or disadvantages with the prior art methods.

We have now found it is possible to characterise individual synthesis particles by reference to random features of the particles.

In a first aspect of the present invention we provide a method for the preparation of a chemical library, which method comprises synthesising the library on a plurality of synthesis particles comprising random features, recording such features during library synthesis, so as to provide a chemical library on a plurality of synthesis particles and wherein the identity of library compound(s) associated with a synthesis particle is established by reference to the particle's random features.

25 By "random features" we mean disordered, physical features of the synthesis particle which arise during manufacture or are subsequently applied to the particle. It will be appreciated that the features may result from an existing manufacturing regime or, preferably, the manufacturing process is adapted to apply random features to the synthesis particles. An optical or other suitable characterisation system is used to categorise individual particles, particles are subsequently tracked according to the same characteristics.

In a set of synthesis particles, each particle will be distinct so that there is no ambiguity when identifying particles at the end of the procedure. It will be appreciated that when the particles are made distinctive by random procedures, there will be a finite chance of two or more identical structures arising by chance. This is acceptable provided that this ambiguity is not inconveniently frequent, this is what is referred to by "distinct". By synthesis particle we mean a bead or other particle upon which library compounds may be synthesised.

By recording, we mean the capturing of sufficient information to define the particle. For convenience, we refer to the information as an image. This may be a literal image or a virtual image constructed from the data that is collected.

10 In a further aspect of the invention we disclose a chemical library provided on a plurality of synthesis particles comprising random features, and wherein the identity of library compound(s) associated with a synthesis particle is established by reference to the particle's random features as recorded during library synthesis.

The chemical library is conveniently prepared by the split synthesis method (Furka *et al* (Abstr. 14th Int. Congr. Biochem., Prague, Czechoslovakia, 1988, 5, 47; Int. J. Pept. Prot. Res, 1991, 37, 487-493) and related procedures where different building blocks are added to a nascent compound at different synthesis stages. It is common in split synthesis procedures, not to mix the particles at the end of the synthesis. In this way information concerning the last building blocks to be added is retained. The method of the invention optionally incorporates
20 this feature to aid identification of the beads of interest.

The invention includes methods where the distribution of beads is random or directed (for example using robotic apparatus), conveniently random.

In a further aspect of the invention we provide a chemical library synthesis system for use with synthesis particles comprising random features, which system comprises chemical
25 library synthesis apparatus coupled to image analysis apparatus such that during chemical library synthesis the image analysis apparatus can capture image(s) of chemical library synthesis particles comprising random features and subsequently identify the particles by reference to their random features.

The coded synthesis particles of the invention are conveniently manipulated using
30 robotic apparatus as disclosed in our co-pending UK patent application no. 9707743.2, filed 17th April 1997, the contents of which are incorporated herein by reference. Advantages of the

use of manipulative robotic devices such as "pick-and-place" machines in combinatorial chemistry include: the ability to form an essentially complete library consisting of a single composite synthesis particle per chemistry either by selection from a larger stochastically formed set or by manipulation of particles at all stages; the ability to select a sub-library of controlled diversity for an initial screen which is designed to highlight the 'volumes of chemical space' in which compounds of interest are to be found, in particular the ability to decide not to select individual particles or sub-libraries of particles — followed by a subsequent selection of further sub-libraries surrounding the regions of interest, without further chemical synthesis processes being required. In this way, the technique significantly enhances the throughput of the overall drug discovery process.

The chemical library may be used in screening methods to identify compounds which modulate the activity of a biological of interest. Typically, a compound will be cleaved from its associated coded particle before testing; alternatively, compounds are tested whilst still attached to their particles. In both cases, there needs to be an association between the measured activity and the particle that gave rise to that activity. Once a particle of interest is identified, its particle code is retrieved, preferably in substantially the same way as was used to track the particle in the course of the synthesis. This code is then compared to the record of the movement of the particles made during the synthesis procedure, and the structure of the compound of interest is inferred. Using appropriate image analysis and computer algorithms, the location of the particle of interest at the various synthesis stages is determined.

Library compounds may be tested in a variety of assay systems. These include biochemical and in vitro assays. In general particle codes are read once the assay is complete and only beads associated with active compounds are identified and decoded. Alternatively library compounds are plated out and decoded before the assay takes place. Active compounds are then identified by reference to their position on the plate(s), for example by reference to plate number and well/locus number.

Convenient assay approaches include the following. The library may be stored in stock solutions (ie. compound is removed from the synthesis particle) for example in wells in microtitre plates. These solutions may be used for many different assays. When activity is detected in an assay, the location of the active compound is determined and the corresponding synthesis particle is retrieved and decoded. Alternatively the synthesis particles are

distributed in a two-dimensional assay system, for example a high density array such as on a gel or in microwells. Compounds are removed from the particles. Any active compounds give rise to zones of activity. Such an approach is disclosed for example in our zone screening UK patent no. 2291708 (Zeneca Limited). Corresponding particles may be
5 decoded, either in situ or by retrieval and transferral to a code reading station.

Conveniently, similar or identical image analysis apparatus is subsequently coupled to chemical library screening apparatus to provide an automated or semi-automated chemical library analysis system wherein synthesis particles comprising random features are identified during or after screening by reference to their images as captured by image analysis apparatus
10 during library synthesis.

Preferred synthesis particles for use in the invention are beads, for example polymeric beads that exhibit features that allow them to be distinguished optically. These features may be intrinsic to the bead, that is conventional beads used for compounds synthesis may be distinguished on the basis of size, shape, surface features, or other such feature or combination
15 of features. Such features will typically result from the manufacturing procedures which, optionally, could be varied in such a way as to enhance the non-uniformity of the beads. For example, surface features (indentations, irregularity) may be introduced as a function of the polymerisation process conditions, such as the choice of surfactants, initiators, cosolvents, reactor configuration and shear rate. A more preferred approach for the production of
20 synthesis particles comprising random features is to facilitate regions of phase separated material (polymer) within the particle matrix. This may be achieved by redispersing a preformed particle into an aqueous medium and then adding additional water insoluble monomer(s) and initiator which will swell into the existing particles. The polymerisation is then completed and will result in regions (domains) of phase separated polymer providing the
25 polymer formed during this additional polymerisation is incompatible with the initial polymer. Ideally this additional monomer phase will include a difunctional or multifunctional unsaturated component (for example di/tri(meth)acrylate or preferably divinyl benzene) which upon polymerisation with the other monomer(s) will form an interpenetrating network (IPN) in the first phase polymer thus ensuring that the phase separated domains remain
30 anchored in a fixed spatial position within the preformed bead.

Preferably, the synthesis particles have features that are introduced during the preparation of the beads. Accordingly, in a further aspect of the invention, we disclose a set of chemical library synthesis particles which comprise random, optically distinguishable features introduced during or after manufacture.

5 By "optically distinguishable features" we mean microparticles, specks, lines, networks, etc., the number and position of which makes each bead distinguishable from the others. By distinguishable we mean that the chances of two or more beads not being distinguishable one from the other is low and does not detract from the usefulness of the method.

10 By "introduced", we mean that these features are incorporated into the bead during manufacture or subsequently at a convenient stage prior to their use in the method of the invention.

The beads are preferably spherical beads of polystyrene or other polymeric material suitable for library synthesis. A convenient size is 100-300 micron but other sizes are
15 possible depending on the number of compounds to be synthesised, scale, economics and other factors. The beads are derivatised for library synthesis using conventional techniques.

Preferably the optically distinguishable features are microparticles. The microparticles may be of any inert, opaque material that may be conveniently imaged. For example the material may be coloured, opaque or of markedly different refractive index to the material
20 comprising the bulk of the bead. The microparticles may be for example in the range 0.5 to 40 micron in diameter. A convenient range would be 3 to 20 microns. The microparticles are incorporated into the bead for example by mixing them into the monomer solution, allowing the monomer to polymerise to beads under conventional conditions. The number of microparticles is adjusted to give the desired number of particles per bead. This may be
25 determined empirically but is expected to be in the range 5 to 200 particles per bead. The optimum number will depend on the microparticle size, the bead size, the resolution of the imaging system, the number of beads in the library and other factors. The optimum number may be determined by routine methods.

By way of example the microparticle may be a preformed polymeric bead made by
30 micro suspension polymerisation ideally having a diameter in the range 5- 15 μm . Such micro beads may be incorporated into the primary bead matrix by suspending them in the

aqueous polymerisation medium and then performing a standard suspension polymerisation with the additional monomer(s). A proportion of the micro beads will become encapsulated within the primary bead structure. There are a number of alternative process strategies that may be adopted. For example, it is preferable that the micro beads are chemically anchored into position within the primary bead matrix. This may be achieved by pre-swelling the micro beads either in aqueous suspension or other medium with monomer preferably containing a multifunctional unsaturated component (for example divinyl benzene). Suspension polymerisation of these monomer swollen micro beads with additional monomer(s) will then yield micro beads linked through an IPN into the bead matrix. The encapsulated micro structures are conveniently distinguished by the use of coloured (dyed or pigmented) or fluorescent components.

The microparticles are conveniently constrained for image capture. This may be achieved for example by passing the particles through a conduit, such as a capillary, this immobilises the particles in two dimensions. The conduit is conveniently translucent and/or has a viewing window. Also, pulsed/stroboscopic lighting may be used to give the impression that a particle is stationary.

Imaging is effected using any convenient means. This is for example achievable using commercially available telescope or long range microscope devices. For example the Questar QM-100 instrument (Box C, New Hope, Pennsylvania 18938, USA) is able to resolve features of 1.1 μm with a field of view from 375 μm to 8mm at a working range of 150mm. It offers a large aperture (c.87mm) which reduces the demands on the overall level of illumination required.

The pattern of microparticles will be random and appear for example like a constellation of stars. Like a constellation, the pattern appears very different depending on the viewing angle. Though it is possible (by bead design, for example by introducing an asicular magnetic particle into the bead it may be aligned to a magnetic field) to orientate the bead during imaging, it is more convenient to take an image at an arbitrary angle. Clearly, if the bead of interest identified after testing is also imaged at a random orientation, it will be difficult in many cases to identify the bead. Hence it is desirable to image the bead of interest from at least two, and up to six different angles, preferably three different angles, for example at or close to 90 degrees apart. The number of images to be taken may depend, in some cases

to a large extent on the transparency of the bead. It will be appreciated that in this embodiment the orientation of the bead is not constant in all imaging steps. This means that a signature may be derived which does not depend on the orientation of the bead. This signature is a distance matrix. A consequence of multiple imaging is a reduction in the number of
5 unique codes. This may be overcome by providing more microparticles to the synthesis beads or by reducing the size of each measured volume element or "voxel".

Having obtained an image, or set of images, of the synthesis particle (bead) techniques familiar to persons skilled in the art may be used to derive the positions of the microparticles within the bead and to define with certainty into which voxel each microparticle will fall. A
10 list of the set of inter-microparticle distances is produced from this data and this is a determining characteristic of the bead. It will be apparent that if the bead is cubic, the familiar cartesian grid is an appropriate co-ordinate frame on which to base the set of distances. Whereas for a spherical bead, a set of spherical co-ordinates is appropriate. A particular advantage of the use of a spherical co-ordinate scheme is that the angular ordinates are not
15 dependent on the bead diameter and thus any bead swelling during exposure to solvents is unlikely to interfere with the overall recognition process. The inter-microparticle distances are conveniently quantised as one of 256 different values. This being convenient for data storage. By way of example based on the measurement of distances between 10 microparticles per bead, 45 bytes of memory may be used to capture the data for each bead.
20 For a 20,000 bead library this is a total of about 1 megabyte of memory. This is not a large data volume by current standards. By way of further example, extra bytes of memory are allocated to each bead to record its movement. Further convenient aspects of the data handling process will be apparent to the artisan of ordinary skill.

In a particular embodiment of the invention the synthesis particles are of diameter 100-
25 300µm and contain between 5 and 200 (preferably between 5 and 25) dispersed microparticles for recognition purposes.

The information content may be increased by the use of particles that differ in size, shape, colour or other recognisable parameter. Furthermore the number of microparticles per bead may be varied. Conveniently this will be achieved by random incorporation of the
30 microparticles during the manufacture of the bead. Alternatively, non-random incorporation may be used to broaden the distribution of number of microparticles per bead. Alternatively,

the microparticles may be incorporated as surface features of the bead, rather than dispersed within the core of the bead.

It will be appreciated that beads may swell differently in different solvents. Hence it is desirable either to use the same solvent for the different imaging stages, or to make

5 allowances for inter-particle spacings with the image analysis software.

The advantages of the method of the invention include the following:

1. Although the synthesis particles are different, the manufacturing process to make them is relatively simple and does not require the particles to be treated differently, i.e. the set of particles may be prepared in one manufacturing sequence.

10 2. The optically introduced features may be introduced to create a large set of beads which are distinguishable one from the other. This allows large compound libraries to be synthesised.

3. The synthesis particles may be imaged by conventional means.

The invention will now be illustrated but not limited by reference to the following

15 Figures wherein:

Figure 1 shows an electron microscope image of a Micropil G-NH₂ bead.

Figure 2 shows an electron microscope image of a GMA bead

Figure 3 shows an electron microscope image of two Pepsyn K beads

- 10 -

CLAIMS

1. A method for the preparation of a chemical library, which method comprises synthesising the library on a plurality of synthesis particles comprising random features,
5 recording such features during library synthesis, so as to provide a chemical library on a plurality of synthesis particles wherein the identity of library compound(s) associated with a synthesis particle is established by reference to that particle's random features.
2. A method as claimed in claim 1 wherein the random features are optically
10 distinguishable.
3. A method as claimed in claim 1 wherein the random features are introduced during or after manufacture of the synthesis particles.
- 15 4. A method as claimed in any preceeding claim wherein the synthesis particles are polymeric beads.
5. A method as claimed in claim 4 wherein the polymeric beads comprise interpenetrating network domains of phase separated polymer as the random features.
20
6. A method as claimed in claim 5 wherein the polymeric beads comprise microparticles as the random features.
7. A method as claimed in any previous claim wherein the synthesis particles comprise
25 glass material and grafted or bonded polymeric material.
8. A method as claimed in any one of claims 1-6 wherein the synthesis particles comprise ceramic material and grafted or bonded polymeric material.
- 30 9. A chemical library prepared according to the process of any preceeding claim.

- 11 -

10. A chemical library synthesis system which comprises chemical library synthesis apparatus coupled to image analysis apparatus such that during chemical library synthesis the image analysis apparatus captures image(s) of chemical library synthesis particles comprising random features and subsequently identifies the particles by reference to their random features.

11. A synthesis system as claimed in claim 10 wherein the synthesis particles are constrained for image capture.

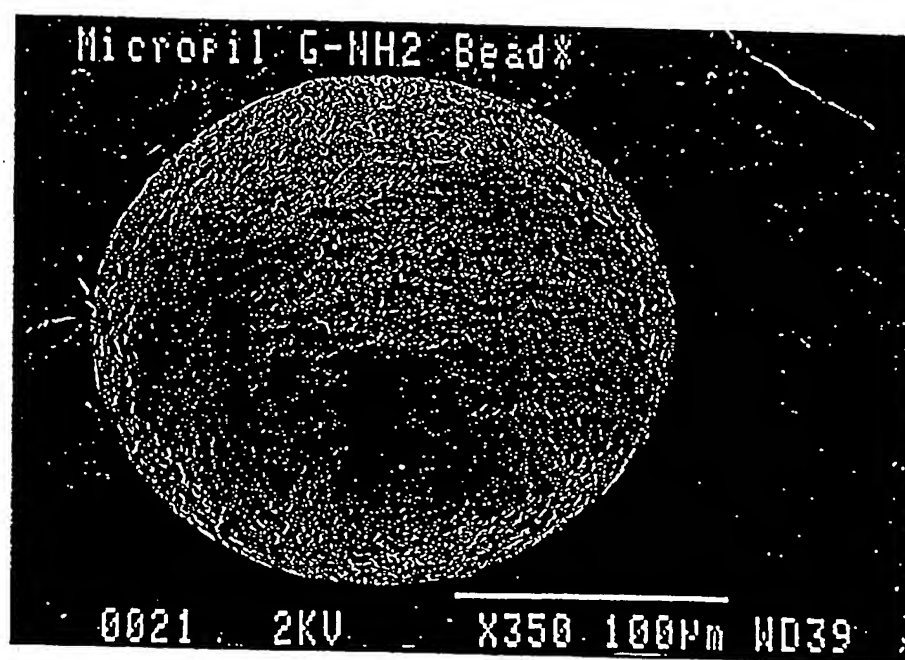
12. A synthesis system as claimed in claim 10 or claim 11 wherein the individual synthesis particle images are not dependent on the orientation of the particles.

13. The use of a chemical library as claimed above in screening methods to identify compounds which modulate the activity of a biological of interest.

14. The use of robotic pick and place apparatus to manipulate synthesis particles as stated in any previous claim.

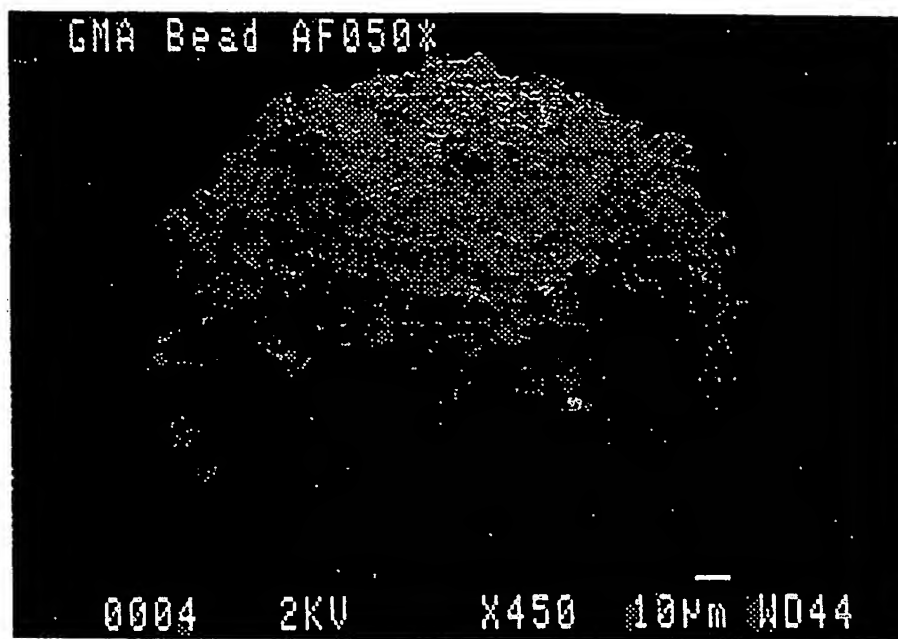
1/3

FIGURE 1



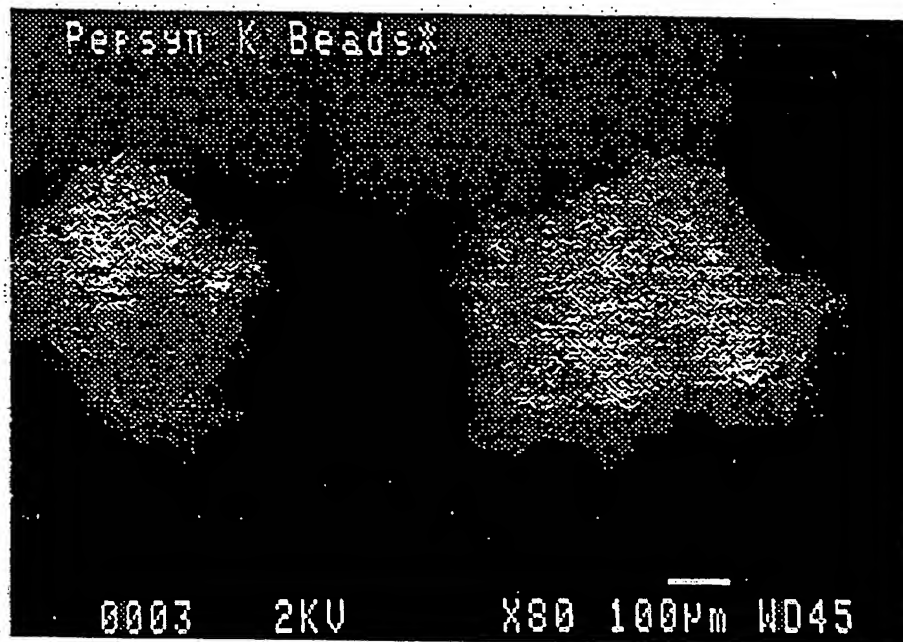
2/3

FIGURE 2



3/3

FIGURE 3



INTERNATIONAL SEARCH REPORT

National Application No
PCT/GB 98/01063

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07B61/00 B01J19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07B B01J C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. C. NICOLAOU: "Radiofrequency encoded combinatorial chemistry" ANGEWANDTE CHEMIE INTERNATIONAL EDITION., vol. 34, no. 20, 1995, pages 2289-2291, XP000535261 WEINHEIM DE cited in the application see the whole document	9, 13
A	---	1-8, 10-12
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

28 July 1998

Date of mailing of the international search report

06/08/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Wright, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/01063

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	E. J. MORAN: "Radio frequency tag encoded combinatorial library method for the discovery of tripeptide-substituted cinnamic acid inhibitors of the protein tyrosine phosphatase PTB1B" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 117, no. 43, 1 November 1995, pages 10787-10788, XP002070500 DC US cited in the application see the whole document	9,13
A	---	1-8, 10-12
A	GB 2 289 150 A (UNIVERSITY OF HERTFORDSHIRE) 8 November 1995 ---	1
P,X	GB 2 306 484 A (UNIVERSITY OF HERTFORDSHIRE) 7 May 1997 see abstract and page 19, lines 1-8	9,13
P,A	-----	1-8, 10-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/01063

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2289150 A	08-11-1995	AU 2081295 A	16-11-1995
		CA 2188386 A	02-11-1995
		EP 0757830 A	12-02-1997
		WO 9529473 A	02-11-1995
		GB 2318666 A, B	29-04-1998
		JP 10504112 T	14-04-1998
<hr/>			
GB 2306484 A	07-05-1997	AU 7318496 A	15-05-1997
		WO 9715390 A	01-05-1997
<hr/>			

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.